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Award Number: W81XWH-05-1-0093

TITLE: Long-Term Outcomes of Alternative Brachytherapy Techniques for Early Prostate Cancer

PRINCIPAL INVESTIGATOR: James A. Talcott, M.D.

CONTRACTING ORGANIZATION: Massachusetts General Hospital
Boston, Massachusetts 02114

REPORT DATE: October 2008

TYPE OF REPORT: Final Addendum

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE *(DD-MM-YYYY)*	**2. REPORT TYPE**	**3. DATES COVERED** *(From - To)*
01-10-2008	Final Addendum	30 DEC 2007 - 29 Sep 2008

4. TITLE AND SUBTITLE

Long-Term Outcomes of Alternative Brachytherapy Techniques for Early Prostate Cancer

5a. CONTRACT NUMBER

5b. GRANT NUMBER
W81XWH-05-1-0093

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
James A. Talcott, M.D.

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

Massachusetts General Hospital
Boston, Massachusetts 02114

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

All active, potentially curative treatments for clinically localized prostate cancer damage quality of life. Brachytherapy, or radioactive seed implants, theoretically may increase the target radiation dose and thus improve control of cancer. It has been rapidly adopted in the U.S. despite limited long-term published outcomes, in part because of its convenience and apparently attractive toxicity profile. However, our recent survey of brachytherapy patients after longer follow-up found surprisingly frequent urinary incontinence and erectile dysfunction. Retrospective evidence suggests that reducing the radiation dose to the urethra may prevent later urinary incontinence. A recent refinement of conventional brachytherapy technique targets only the peripheral zone of the prostate, sharply reducing the dose to the urethra, and attempts to reduce radiation "cold spots" by using intraoperative feedback from real-time magnetic resonance imaging (MRI). Using our validated cancer-specific scales, our pilot data suggested that the altered brachytherapy technique had the intended benefit but also unexpected outcomes. We have extended our cohort study of 276 brachytherapy patients and now compare 3- and 24-month outcomes of this technique to standard ultrasounded-guided brachytherapy.

15. SUBJECT TERMS
Quality of Life, Outcomes, bowel symptoms, sexual function, questionnaires, magnetic resonance imaging

16. SECURITY CLASSIFICATION OF:			**17. LIMITATION OF ABSTRACT**	**18. NUMBER OF PAGES**	**19a. NAME OF RESPONSIBLE PERSON**
a. REPORT	**b. ABSTRACT**	**c. THIS PAGE**			USAMRMC
U	U	U	UU	21	**19b. TELEPHONE NUMBER** *(include area code)*

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BACKGROUND

Prostate cancer is a unique malignancy because of the uncertain but probably modest efficacy of available local treatments for early (non-metastatic) cancer, the potential for long-lasting treatment-related urinary, bowel and sexual function problems, its unusually long typical natural history. As a result the great majority of patients experience any permanent symptoms for more than a decade, and its great impact on the American population, the highest incidence and second highest prevalence of any non-cutaneous malignancy in the United States (1). The most recent estimate is over 1.8 million men. Nearly one million had survived 5 years and a quarter million 10 years or more. Most men are diagnosed with early (non-metastatic) cancer, for which local therapy may be curative, but because of the prostate's anatomical location may lead to sexual, urinary and bowel dysfunction (2-6). The great majority of these men will be treated with either external beam radiation therapy (XRT), radical prostatectomy (RP), or ultrasound guided interstitial prostate radiation therapy (BT), also known as brachytherapy or seed implants. BT is now widely available, despite still sparse efficacy data (7, 8). Complication rates of the alternative local treatments differ qualitatively and quantitatively. All active treatments for prostate cancer produce erectile dysfunction (ED) in most men, and long-term urinary incontinence (after RP and brachytherapy) and bowel dysfunction (after EBRT) are common (3, 5, 6, 9-14).

Although early experience with brachytherapy using freehand placement of radioactive seeds in open pelvic surgery yielded both unsatisfactory control of cancer and high post-treatment complication rates (15-18), a percutaneous ultrasound-guided technique developed by Blasko, Ragde and colleagues in Seattle dramatically improved three-dimensional radiation dose distributions (13-15). As a result, brachytherapy was reevaluated (7), resulting in its now wide availability in the United States (19). Randomized comparisons between modalities are rare and flawed, although a randomized trial of RP vs. initial observation has recently found evidence of a small benefit for surgery (20, 21) at a cost in quality of life (22). Retrospective, prognostically-stratified comparisons of RP to XRT have appeared (23, 24), and more recently one between ultrasound-guided brachytherapy and RP or XRT (8). Based on a multivariable time to PSA failure analysis of patients stratified by previously-defined pretreatment risk groups, low risk patients ($T_{1c, 2a}$ and PSA $\leq$ 10 and Gleason $\leq$ 6) had comparable PSA failure free survival at 5 years after RP, XRT, or brachytherapy, but brachytherapy patients at high (T_{2c} or PSA > 20 or Gleason $\geq$ 8) or intermediate risk (T_{2b} or Gleason 7 or PSA > 10 and $\leq$ 20) had significantly worse cancer control than patients managed with RP or XRT.

BT, like other prostate cancer treatments, affects patient quality of life. Our team documented one of the most important complications, the risk of long-term urinary incontinence. Although acute urethral irritation and urinary obstruction are well-documented short-term complications of standard ultrasound-guided BT (27-33), reports by treating physicians after relatively short follow-up (median 18-45 months) indicates little evidence of long-term complications (27-29, 31, 34). However, because of the potentially long delay after brachytherapy for some symptoms, especially urinary incontinence and erectile dysfunction (ED), and the usually greater complication rates obtained directly from patients rather than treating physicians, in part because of patients' reluctance to complain to their doctors (2, 5, 6, 11, 35), we felt these reports may underreport long-term complications of BT, especially urinary incontinence and erectile dysfunction. However, there is some evidence that the bowel problems associated with external beam radiation therapy (EBRT) are less frequent in BT.

To better define long-term BT-associated side effects, we performed a cross sectional survey of the earliest large patient cohort treated by the Seattle group completed at a median of 5 years after treatment. We found that 38% of BT patients who had not had comorbid procedures like transurethral resection of the prostate (TURP) reported some degree of urinary incontinence. These results may be partly explained by the older age of the patients in that early cohort (median: 75 years) and by preexisting pretreatment dysfunction our cross-sectional survey could not document. However, the outcome is consistent with the phenomenon of acute urethral necrosis the Seattle physician group had previously described (36), and the prevalence of urinary incontinence we found is much higher than expected in men in that age group. Subsequent retrospective studies supported the belief that the primary risk factor producing long-term incontinence is the proportion of the urethra receiving high-dose radiation (31, 37). Reduced radiation to the urethra was subsequently associated with reduced incontinence (38). The MRIBT technique addresses this problem by excluding the periurethral transition zone of the prostate from the target volume for radiation, trading the risk of allowing cancer in the transition zone to persist after treatment in exchange for decreased urethral irradiation in the hope that late urinary incontinence will also be decreased. Because cancers in the transition zone are much less frequent than those in the peripheral zone and may have a more indolent course, this technical change may benefit patients overall, although the benefit and harms require empirical verification. This project follows on a recently completed project, Outcomes of Alternative Brachytherapy Techniques for Early Prostate Cancer (DAMD17-02-1-0090), to determine whether a quality of life benefit can be demonstrated in the first 2 years after BT. The current project continues that project for an additional 3 years. Unfortunately, the first project was delayed by 10 months for DAMD IRB review of the project, which had previously been approved by all participating institutions' own IRBs. Therefore, follow-up is delayed by that amount. We present interim results from the new study, which closely overlap the results we presented in the Final Report of the earlier project.

METHODS

Patient Population

Patients are recruited from 3 Boston-area treatment programs directed by three outstanding brachytherapy experts: Brigham and Women's Hospital (BWH), directed by Dr. Anthony D'Amico, the Massachusetts General Hospital (MGH), directed by Dr. Anthony Zietman, and Beth Israel –Deaconess (BID) and MetroWest Hospitals, both directed by Dr. Irving Kaplan. The first 3 sites are in Boston, MA, and the fourth in suburban Framingham, MA. Before treatment, investigators or study staff at the Massachusetts General Hospital Center for Outcomes Research give or send all eligible patients the baseline study instrument, along with a cover letter describing the study from the Principal Investigator and their treating physician. The few patients who do not respond within two weeks are contacted by telephone. Enrolled patients are registered with the Quality Assurance Office for Clinical Trials (QAOCT) at the Dana Farber Cancer Institute by study staff.

At each specified follow-up interval from initiation of therapy, 3, 12, 24, 36, 48 and 60 months, we mail patients a cover letter and follow-up questionnaires containing the same instruments as the pretreatment baseline questionnaire, along with postage paid return envelopes. Data are collected by the staff of the Center for Outcomes Research at Massachusetts General Hospital. Using an in-house relational database system, study participants are assigned a unique

study identification number used to track the patients until follow-up is complete or the patient drops out of the study. Automated follow-up procedures flag when participants should receive a postcard, follow-up mailing, or telephone call. Weekly statistical reports detail the status of respondents. Data management is performed at QAOCT, the data management center for all studies of the Dana Farber/Partners Cancer Care. The QAOCT data manager confirm eligibility, register patients and ensure that study parameters are followed.

Data Collection

Patients are asked to complete self-administered questionnaires that include assessments of sexual function, urinary and bowel complications of treatment, and disease-focused quality of life we previously validated (39, 40). An experienced genitourinary oncology research nurse abstracts information from medical records regarding demographic characteristics, cancer prognostic factors, comorbid diseases, treatments and subsequent clinical course using the forms developed in earlier studies.

1. Urinary, Sexual and Bowel Function. Patient-completed questionnaires included four symptom indices to assess urinary incontinence, urinary obstruction/irritation, bowel dysfunction, and sexual dysfunction. We reported previously the clinical derivation of these indices and psychometric evaluation of their reliability, validity, and responsiveness to treatment effects.(references) The Urinary Incontinence Index contains 3 questions gauging the degree of urinary control. The Urinary Obstruction and Irritation Index contains 5 questions assessing hesitancy, frequency, nocturia, dysuria, and urgency. Sexual function was measured by a core set of validated items and scales that assess patients' perceptions of their erectile function, and the quality of orgasm and ejaculation. This core set of items will be augmented by items that assess interest in sexual activity (i.e., libido), frequency of sexual activity, and satisfaction with sexual activity. In addition, we administered the five-item sexual function/quality of life scale developed in the Medical Outcomes Study (reference), also used in our previous studies. The internal consistency of this scale in early prostate cancer patients is very high (α =.90). Bowel Problems items include diarrhea, urgency of bowel movements, rectal pain, bleeding, passing mucus, abdominal cramping, and tenesmus.

Each index was scored by summing the component items and then standardizing that value to vary from 0 (no dysfunction) to 100 (maximum dysfunction).

RESULTS

As of December 2009, the project recruited a total of 296 patients, of whom 10 (3%) were found to be ineligible for the following reasons: patient chose a different treatment after enrolling (3 patients), chose to receive external beam radiation in addition to brachytherapy (3 patients), had had prior treatment (3 patients) or completed his baseline questionnaire after receiving brachytherapy (1 patient). The remaining 286 eligible patients included 209 in the two ultrasound-guided "conventional" brachytherapy treatment groups (110 patients in $USBT_1$ and 99 patients in $USBT_2$) and 77 patients in the MRI-guided treatment group (MRIBT). Each patient completed the baseline questionnaire (See Appendix, Baseline Questionnaire) before treatment. Follow-up questionnaires have been received and entered into the database as follows: 244 1-Month Questionnaires (85% of the 286 enrolled and eligible patients now at least 1 month after treatment, including 16 patients who dropped out of the study before the first follow-up questionnaire), 254 3-Month Questionnaires (88% of 286 eligible patients with at least 3 months follow-up, with 24 total dropouts), 248 12-Month Questionnaires (87% of 286 patients 12

months out, with 36 total dropouts), 232 24-Month Questionnaires (83% of 278 eligible patients 24 months out, with 36 total dropouts), 201 36-Month Questionnaires (78% of 259 living, eligible patients 36 months out, with 39 total dropouts), 141 48-Month Questionnaires (64% of 220 living, eligible patients 48 months out, with 49 total dropouts), and 86 60-Month Questionnaires (59% of 146 living, eligible patients 60 months out, with 49 total dropouts). Three patients died before the 36-month follow-up and 2 patients died before the 60-month follow-up. The response rate is reduced in the most recent periods (36-month, 48-month, and 60-month) because all earlier dropouts are recorded prior to initial survey requests: e.g., the first returned 60-month survey represented 1 of 50, or 2%, because of the prior 49 dropouts. The study retention has been very good, with only 25 patients (10%) dropping out after 3-month follow-up, although additional 33 patients have not returned their most recent questionnaire, including 27 patients who received it more than 1 month ago and may have dropped out of the study. We report the results of the analysis as of January 1, 2009.

Pretreatment characteristics. The 286 eligible enrolled patients include 77 patients who received the experimental MRI-guided technique (MRBT) and 209 patients receiving conventional ultrasound-guided brachytherapy (USBT), 110 patients treated by one physician ($USBT_1$) and 99 patients treated by another ($USBT_2$). Of these, 24 patients (84%) failed to complete 3-month follow-up, including 15 patients who dropped out before the 1-month follow-up and another 9 patients who dropped out before the 3-month follow-up, leaving a total of 262 patients with at least 3 months of follow-up, of whom 73 patients received the experimental MRI-guided technique (MRBT) and another 189 patients who received conventional ultrasound-guided brachytherapy (SBT), 98 patients treated by one physician ($USBT_1$) and 91 patients treated by another ($USBT_2$) (Table 1). This group will be the focus of this analysis.

Patients in the MRBT treatment group were younger than the USBT group (median: 65.3 years vs. 68.3 years, P=0.005), and the $USBT_2$ younger than the $USBT_1$ group (median: 67.1 years vs. 69.9 years, P=0.004). Over 95% were Caucasian. More than three-fourths were currently married at study enrollment and had attended at least some college, and more than one fourth had graduate degrees. However, the MRBT patients had significantly higher educational attainment, with more than half holding a graduate of professional degree.

While the treatment groups were similar in pretreatment PSA levels, Gleason score and risk group, the proportion of patients in the MRBT group with non-palpable (T1) cancers was greater (98% vs. 92%, P=0.05).

Functional Outcomes. Because of occasional omitted responses and incomplete, ongoing data entry, change scores for treatment-related dysfunction could be calculated for at most 208 of the 262 enrolled patients with at least 3 months follow-up.

Urinary Dysfunction. Study patients had little reported urinary incontinence or bowel problems before treatment, with all mean baseline dysfunction scores less than 5 (Table 2). However, urinary obstruction/irritation was evident, and patients reported even more sexual dysfunction, with less pretreatment dysfunction for the MRBT group in both categories. Further, the MRBT patient group had less increase at 3 months in both urinary obstruction/irritation (mean scale change difference: 8.7 vs. 25.7; P = 0.0000) and incontinence (13.0 vs. 17.2; P=0.035). These benefits continued to be statistically significant or nearly so through 24 months, but progressively smaller sample sizes and resolution of acute symptoms resulted in lesser differences that did not achieve statistical significance thereafter in follow-up so far (Tables 2-7).

Of interest, given the prevalence of late-appearing urinary incontinence we and others have documented, there is evidence suggesting an increase in urinary incontinence scores in all patient groups in 60-month vs. 48-month follow-up (mean: 12.5 vs. 9.5) but given the incomplete follow-up, these comparisons have little statistical power.

Bowel problems. Because our pilot study had indicated greater bowel dysfunction from the MRBT technique, we anticipated similar results in the current study. However, we found little evidence to support our previous observation. At no follow-up time did MRBT patients report more bowel problems.

Sexual dysfunction. While the MRBT patients had better pretreatment function (mean: 22.6 vs. 37.9; P=0.003), which persisted through the first 24 months, there were no differences between MRIBT and USBT patients' post-treatment change in sexual dysfunction at any time period.

Comparison of the two USBT treatment groups. Surprisingly, we found some differences in symptom outcomes not only between the MRIBT and USBT groups, but also between the USBT treatment groups. In particular, mean changes in acute urinary obstruction/irritation were greater in the $USBT_2$ group compared to the $USBT_1$ at 3-month follow-up (change: 30.0 vs. 21.8; P= 0.02), and a similar trend was echoed in the urinary incontinence scale (change: 11.9 vs. 7.3; P= 0.12). However, these differences had disappeared as acute symptoms largely remitted by the 12-month follow-up point. We have begun an investigation of potential explanatory factors, including a time-series analysis of changes in outcomes after modified technique in the $USBT_2$ treatment group.

CONCLUSIONS

Our study, with as yet incomplete 5-year follow-up, adds substantial new information to the question of whether modifying brachytherapy technique can improve functional outcomes by reducing treatment-related toxicity. Our results provide gratifying confirmatory evidence that the MRIBT technique, which sharply reduces radiation dose to the periurethral transition zone of the prostate, produces the intended reduction in short-term urinary symptoms of a statistically and most likely clinically significant (mean change in urinary obstruction/irritation scale score at 3-month follow-up: 17.0, approximately 1 SD) magnitude, at least for some patients, measured by both urinary incontinence and urinary obstruction/irritation scales. These results are consistent with our earlier observation, made in a far less satisfactory study population (42). While reassuring and indicating potential relief from the threat of worsened short-term symptoms of urinary obstruction/irritation and presumably decreased risk of potentially very painful complete urinary obstruction, the early reduction in urinary symptoms, especially obstruction/irritation do not directly address what many consider the most serious urinary problem caused by brachytherapy, the risk of long-term urinary incontinence, the presumed consequence of acute urethral necrosis, described by Blasko and colleagues in the pioneering Seattle brachytherapy group (27). We have argued elsewhere that since the magnitude or these urinary symptoms is primarily determined by the same cause, the intensity and extent of urethral radiation, it is reasonable to consider short-term urinary symptoms, especially when parallel results parallel results are found using 2 distinct, validated measures of urinary function (42). However we have found only modest evidence of the onset of late incontinence in any group in this analysis. We hope that we will be able to continue follow-up on this population, which would be very helpful

to fully to fully evaluate the relative risk of late urinary incontinence for patients undergoing not only the experimental MRIBT technique but contemporary standard USBT technique.

However, other results are less consistent with our earlier report. We found little evidence that MRIBT patients experience greater treatment-induced bowel problems compared to USBT patients nor that they experience less sexual dysfunction, as we had reported earlier (42). The latter result was disconcerting, because of the better pretreatment sexual function of the MRIBT patient group, a possible indicator or lesser vulnerability to treatment-induced dysfunction but also creating a greater potential for functional loss. However, the potential for confounding implied in noting the better MRIBT patients' baseline sexual function suggests an alternate explanation for the earlier observation. While the MRIBT patient group at baseline gave evidence of self-selection that might lead to better functional outcomes, those differences were much greater in the earlier study population (42). Therefore, the earlier observation may have simply reflected confounding by treatment indication, as we noted in the earlier report.

Finally, however, to our surprise, we found differences of comparable magnitude *between* USBT subgroups in the mean increases in both urinary dysfunction scales at 3 months follow-up, suggesting that factors other than the MRIBT technique's planned reduction in periurethral radiation can produce substantial differences in short-term treatment-related urinary symptoms. This entirely unexpected result is however conceptually plausible, in its implication that the results of a complex medical technology differs in its results depending on the treatment team and other unspecified factors. Given the complexity of prostate brachytherapy, such variability should be expected. The variability in functional outcomes between USBT groups obscured differences between MRIBT and USBT by increasing variability in the outcome measures. However, it provides an additional line of investigation, which we plan to pursue, examining factors that may be associated with variations in patient outcomes within USBT patient subgroups.

Summary. Our initial comparison of functional outcomes provides support for both our earlier observations and the guiding assumption that motivated the development of the MRIBT technique, the belief that avoiding urethral irradiation can importantly ablate acute treatment-related urinary symptoms, and provides hope that such changes can attenuate long-term urinary incontinence, due to acute urethral necrosis, a likely related and perhaps more serious treatment-related quality of life problem. However, we have as yet found only modest evidence of late urinary incontinence, arising between 48-month and 60-month follow-up reports. We found no support for our other earlier observations that MRIBT increases treatment-related bowel dysfunction or decreases treatment-related sexual dysfunction, although our current results suggest that confounding may have accounted for the earlier observations, as we had suggested. Finally, the substantial differences in outcomes between USBT subgroups raise the possibility of identifying important additional factors that may increase of attenuate the treatment-related complications of brachytherapy.

Abbreviations

CT	computed tomography
CTV	clinical target volume
DVH	dose volume histogram
MR	magnetic resonance
MRI	magnetic resonance imaging
MRIBT	magnetic resonance image guided prostate brachytherapy
MRI	magnetic resonance imaging
PSA	prostate-specific antigen
XRT	radiation therapy
PR	radical prostatectomy

REFERENCES

1. Hewitt M, Greenfield S, Stovall E, editors. From cancer patient to survivor: lost in transition. Washington, DC: The National Academies Press; 2005.
2. Fowler FJ, Jr., Barry MJ, Lu-Yao G, Roman A, Wasson J, Wennberg JE. Patient-reported complications and follow-up treatment after radical prostatectomy. The National Medicare Experience: 1988-1990 (updated June 1993). Urology 1993;42:622-9.
3. Litwin MS, Hays RD, Fink A, Ganz PA, Leake B, Leach GE, et al. Quality-of-life outcomes in men treated for localized prostate cancer. JAMA 1995;273:129-35.
4. Beard CJ, Propert KJ, Rieker PP, Clark JA, Kaplan I, Kantoff PW, et al. Complications after treatment with external-beam irradiation in early-stage prostate cancer patients: a prospective multiinstitutional outcomes study. J Clin Oncol 1997;15:223-9.
5. Talcott JA, Rieker P, Propert KJ, Clark JA, Wishnow KI, Loughlin KR, et al. Patient-reported impotence and incontinence after nerve-sparing radical prostatectomy. J Natl Cancer Inst 1997;89:1117-23.
6. Talcott JA, Rieker P, Clark JA, Propert KJ, Weeks JC, Beard CJ, et al. Patient-reported symptoms after primary therapy for early prostate cancer: results of a prospective cohort study. J Clin Oncol 1998;16:275-83.
7. D'Amico AV, Coleman CN. Role of interstitial radiotherapy in the management of clinically organ-confined prostate cancer: the jury is still out. J Clin Oncol 1996;14:304-15.
8. D'Amico AV, Whittington R, Malkowicz SB, Schultz D, Blank K, Broderick GA, et al. Biochemical outcome after radical prostatectomy, external beam radiation therapy, or interstitial radiation therapy for clinically localized prostate cancer. JAMA 1998;280:969-74.
9. Potosky AL, Legler J, Albertsen PC, Stanford JL, Gilliland FD, Hamilton AS, et al. Health outcomes after prostatectomy or radiotherapy for prostate cancer: results from the Prostate Cancer Outcomes Study. J Natl Cancer Inst 2000;92:1582-92.
10. Hamilton AS, Stanford JL, Gilliland FD, Albertsen PC, Stephenson RA, Hoffman RM, et al. Health outcomes after external-beam radiation therapy for clinically localized prostate cancer: results from the Prostate Cancer Outcomes Study. J Clin Oncol 2001;19:2517-26.
11. Fowler FJ, Jr., Barry MJ, Lu-Yao G, Wasson JH, Bin L. Outcomes of external-beam radiation therapy for prostate cancer: a study of Medicare beneficiaries in three surveillance, epidemiology, and end results areas. J Clin Oncol 1996;14:2258-65.
12. Fowler FJ, Jr., Barry MJ, Lu-Yao G, Wasson J, Roman A, Wennberg J. Effect of radical prostatectomy for prostate cancer on patient quality of life: results from a Medicare survey. Urology 1995;45:1007-13; discussion 1013-5.
13. Talcott JA, Clark JA, Stark PC, Mitchell SP. Long-term treatment related complications of brachytherapy for early prostate cancer: a survey of patients previously treated. J Urol 2001;166:494-9.
14. Talcott JA, Manola J, Clark JA, Kaplan I, Beard CJ, Mitchell SP, et al. Time course and predictors of symptoms after primary prostate cancer therapy. J Clin Oncol 2003;21:3979-86.
15. Whitmore WF, Jr., Hilaris B, Grabstald H. Retropubic implantation to iodine 125 in the treatment of prostatic cancer. J Urol 1972;108:918-20.
16. Carlton CE, Jr., Dawoud F, Hudgins P, Scott R, Jr. Irradiation treatment of carcinoma of the prostate: a preliminary report based on 8 years of experience. J Urol 1972;108:924-7.
17. Kuban DA, el-Mahdi AM, Schellhammer PF. I-125 interstitial implantation for prostate cancer. What have we learned 10 years later? Cancer 1989;63:2415-20.
18. Gottesman JE, Tesh DG, Weissman WD. Failure of open radioactive 125iodine implantation to control localized prostate cancer: a study of 41 patients. J Urol 1991;146:1317-9; discussion 1319-20.
19. Blasko JC, Lange PH. Prostate cancer--the therapeutic challenge of locally advanced disease [editorial; comment]. N Engl J Med 1997;337:340-1.
20. Holmberg L, Bill-Axelson A, Helgesen F, Salo JO, Folmerz P, Haggman M, et al. A randomized trial comparing radical prostatectomy with watchful waiting in early prostate cancer. N Engl J Med 2002;347:781-9.
21. Bill-Axelson A, Holmberg L, Ruutu M, Haggman M, Andersson SO, Bratell S, et al. Radical prostatectomy versus watchful waiting in early prostate cancer. N Engl J Med 2005;352:1977-84.
22. Steineck G, Helgesen F, Adolfsson J, Dickman PW, Johansson JE, Norlen BJ, et al. Quality of life after radical prostatectomy or watchful waiting. N Engl J Med 2002;347:790-6.

23. Kupelian PA, Katcher J, Levin HS, Klein EA. Stage T1-2 prostate cancer: a multivariate analysis of factors affecting biochemical and clinical failures after radical prostatectomy. Int J Radiat Oncol Biol Phys 1997;37:1043-52.
24. D'Amico AV, Whittington R, Kaplan I, Beard C, Jiroutek M, Malkowicz SB, et al. Equivalent biochemical failure-free survival after external beam radiation therapy or radical prostatectomy in patients with a pretreatment prostate specific antigen of > 4-20 ng/ml. Int J Radiat Oncol Biol Phys 1997;37:1053-8.
25. Prete JJ, Prestidge BR, Bice WS, Dubois DF, Hotchkiss LA. Comparison of MRI- and CT-based post-implant dosimetric analysis of transperineal interstitial permanent prostate brachytherapy. Radiat Oncol Investig 1998;6:90-6.
26. D'Amico AV, Cormack R, Tempany CM, Kumar S, Topulos G, Kooy HM, et al. Real-time magnetic resonance image-guided interstitial brachytherapy in the treatment of select patients with clinically localized prostate cancer. Int J Radiat Oncol Biol Phys 1998;42:507-15.
27. Blasko JC, Grimm PD, Ragde H. Brachytherapy and organ preservation in the management of carcinoma of the prostate. Sem Rad Oncol 1993;3:240-9.
28. Dattoli M, Wallner K, Sorace R, Koval J, Cash J, Acosta R, et al. 103Pd brachytherapy and external beam irradiation for clinically localized, high-risk prostatic carcinoma. Int J Radiat Oncol Biol Phys 1996;35:875-9.
29. Stock RG, Stone NN, De Wyngaert JK, Lavagnini P, Unger PD. Prostate specific antigen findings and biopsy results following interactive ultrasound guided transperineal brachytherapy for early stage prostate carcinoma. Cancer 1996;77:2386-92.
30. Nag S, Scaperoth DD, Badalament R, Hall SA, Burgers J. Transperineal palladium 103 prostate brachytherapy: analysis of morbidity and seed migration. Urology 1995;45:87-92.
31. Wallner K, Roy J, Harrison L. Tumor control and morbidity following transperineal iodine 125 implantation for stage T1/T2 prostatic carcinoma. J Clin Oncol 1996;14:449-53.
32. Zelefsky MJ, Wallner KE, Ling CC, Raben A, Hollister T, Wolfe T, et al. Comparison of the 5-year outcome and morbidity of three-dimensional conformal radiotherapy versus transperineal permanent iodine-125 implantation for early-stage prostatic cancer. J Clin Oncol 1999;17:517-22.
33. Brandeis JM, Litwin MS, Burnison CM, Reiter RE. Quality of life outcomes after brachytherapy for early stage prostate cancer. J Urol 2000;163:851-7.
34. Critz FA, Tarlton RS, Holladay DA. Prostate specific antigen-monitored combination radiotherapy for patients with prostate cancer. I-125 implant followed by external-beam radiation. Cancer 1995;75:2383-91.
35. Litwin M. Health-related quality of life after treatment for localized prostate cancer. Cancer 1995;75:2000-2003.
36. Blasko JC, Grimm PD, Ragde H. Brachytherapy and organ preservation in the management of carcinoma of the prostate. Semin Radiat Oncol 1993;3:240-249.
37. Hu K, Wallner K. Urinary incontinence in patients who have a TURP/TUIP following prostate brachytherapy. Int J Radiat Oncol Biol Phys 1998;40:783-6.
38. Wallner K, Lee H, Wasserman S, Dattoli M. Low risk of urinary incontinence following prostate brachytherapy in patients with a prior transurethral prostate resection. Int J Radiat Oncol Biol Phys 1997;37:565-9.
39. Clark JA, Talcott JA. Symptom indexes to assess outcomes of treatment for early prostate cancer. Med Care 2001;39:1118-30.
40. Clark JA, Bokhour BG, Inui TS, Silliman RA, Talcott JA. Measuring patients' perceptions of the outcomes of treatment for early prostate cancer. Med Care 2003;41:923-36.
41. Stewart A, Ware J, Jr. Measuring function status and well-being: The Medical Outcomes Study Approach. Durham: Duke University Press; 1992.
42. Seo PH, D'Amico AV, Clark JA, Kaplan I, Manola JB, Mitchell SP, et al. Assessing a prostate cancer brachytherapy technique using early patient-reported symptoms: a potential early indicator for technology assessment? Clin Prostate Cancer 2004;3:38-42.

TABLES

Table 1. Sociodemographic and clinical characteristics of 262 eligible patients with early prostate cancer who underwent brachytherapy and completed at least 3 month follow-up.

Characteristic	Level	MRI-guided BT	All U/S-guided BT	U/S-guided BT (1)	U/S-guided BT (2)	P-value†
Number of patients		73	189	98	91	
Age	Median	65.3	68.3	69.9	67.1	0.005
	Mean	65.1	67.5	68.8	66.1	*0.004*
	Range	42.5-81.7	50.9-81.7	52.2-81.7	50.9-79.3	
Ethnic group	Caucasian	69 (96)	182 (97)	91 (96)	88 (97)	0.84
	African-American	3 (4)	5 (3)	3 (3)	2 (2)	*1.0*
	Asian	0 (0)	2 (1)	1 (1)	1 (1)	
	Unknown (n)	0	3	3	0	
Marital status	Single	3 (4)	10 (5)	5 (5)	5 (5)	0.97
	Currently married	56 (78)	146 (78)	74 (75)	72 (79)	*0.89*
	Separated, divorced or widowed	13 (18)	32 (17)	18 (19)	14 (15)	
	Unknown (n)	1	1	1	0	
Highest education, number (%)	Completed high school or less	6 (8)	47 (25)	22 (23)	20 (23)	0.000
	Attended college	27 (38)	89 (47)	46 (48)	43 (49)	*1.0*
	Graduate/professional degree	39 (54)	53 (28)	28 (29)	25 (28)	
	Unknown (n)	1	5	2	3	
Pretreatment PSA, ng/ml	Median	5.0	5.5	4.9	5.4	0.23
	Mean	5.2	5.5	5.3	5.8	*0.07*
	Range	0.8-13.3	0.6-13.5	0.6-13.5	0.7-12.0	
Pretreatment PSA range	<10ng/ml	71 (95)	176 (95)	89 (94)	87 (96)	
	10-20ng/ml	2 (3)	9 (5)	5 (5)	4 (4)	
	>20ng/ml	0 (0)	0 (0)	0 (0)	0 (0)	
Gleason score	5	0 (0)	2 (1)	2 (2)	0 (0)	0.90
	6	62 (85)	148 (81)	73 (80)	75 (82)	*0.58*
	7	11 (15)	31 (17)	15 (16)	16 (18)	
	8	0 (0)	1 (1)	1 (1)	0 (0)	
Clinical stage	Not palpable (T1)	72 (98)	170 (92))	87 (93)	83 (91)	0.05
	Palpable (T2)	1 (1)	15 (8)	7 (7)	8 (9)	*0.79*
Risk group	Low	60 (82)	144 (79)	72 (79)	72 (79)	0.81
	Intermediate	13 (18)	37 (20)	18 (20)	19 (21)	*1.0*

High	0 (0)	1 (1)	1 (1)	0 (0)

†MRI-guided vs. ultrasound (U/S)-guided brachytherapy (BT). P-values *in italics* are for U/S-guided BT (1) vs U/S-guided BT (2.)

Table 2. Mean treatment-related function scores at baseline, at 3 months after treatment and changes from baseline to 3 months for patients who completed responses at baseline and at 3-month follow-up.

	Patients Responding	Baseline Score	Baseline (SD)	3 Months Score	3 Months (SD)	Baseline to 3 mo. Change Score	Baseline to 3 mo. Change (SD)	P-value
Urinary obstruction/irritation								
Ultrasound-guided Brachytherapy	125	17.2	(11.3)	42.9	(20.4)	25.7	20.3	0.0000
Hospital 1	66	16.7	(10.3)	38.5	(19.0)	21.8	18.4	*0.02*
Hospital 2	59	17.9	(12.4)	47.9	(20.9)	30.0	20.9	
MRI-guided Brachytherapy	57	22.9	(12.5)*	31.6	(15.9)***	8.7	12.1	
All patients	182	19.0	(12.0)	39.3	(19.8)	20.3	19.6	
Urinary incontinence								
Ultrasound-guided Brachytherapy	139	2.7	(7.3)	12.3	(18.1)	9.6	17.2	0.006
Hospital 1	71	2.5	(6.9)	9.9	(16.6)	7.3	16.1	*0.12*
Hospital 2	68	2.9	(7.7)	14.9	(19.4)	11.9	18.1	
MRI-guided Brachytherapy	56	4.8	(11.1)	7.3	(15.8)*	2.5	13.0	
All patients	195	3.3	(8.6)	10.9	(17.6)	7.5	16.4	
Bowel problems								
Ultrasound-guided Brachytherapy	149	3.6	(6.0)	9.1	(10.0)	5.4	10.1	0.79
Hospital 1	74	3.1	(4.5)	7.9	(9.5)	4.7	9.1	*0.41*
Hospital 2	75	4.1	(7.1)	10.2	(10.3)	6.1	11.1	
MRI-guided Brachytherapy	59	4.1	(5.5)	9.1	(9.9)	5.1	10.0	
All patients	208	3.8	(5.8)	9.1	(9.9)	5.3	10.0	
Sexual function								
Ultrasound-guided Brachytherapy	135	37.9	(38.3)	49.0	(35.5)	11.1	28.1	0.79
Hospital 1	71	42.7	(39.1)	50.9	(36.8)	8.1	23.1	*0.20*
Hospital 2	64	32.6	(37.0)	46.9	(34.0)	14.3	32.7	
MRI-guided Brachytherapy	56	22.6	(30.8)***	32.5	(33.3)***	9.9	24.5	
All patients	191	33.4	(36.9)	44.2	(35.6)	10.7	27.1	

Table 3. Mean treatment-related function scores at baseline, at 12 months after treatment and changes from baseline to 12 months for patients who completed responses at baseline and at 12-month follow-up.

	Patients Responding	Baseline Score	Baseline (SD)	12 Months Score	12 Months (SD)	Baseline to 12 month change Score	Baseline to 12 month change (SD)	P-value
Urinary obstruction/irritation								
Ultrasound-guided Brachytherapy	123	17.5	(11.1)	26.9	(15.4)	9.4	(15.6)	0.001
Hospital 1	64	16.9	(10.0)	26.5	(14.5)	9.5	(15.9)	*0.94*
Hospital 2	59	18.0	(12.2)	27.4	(16.4)	9.3	(15.3)	
MRI-guided Brachytherapy	54	22.9	(12.4)*	24.2	(13.9)	1.2	(15.4)	
All patients	177	19.1	(11.8)	26.1	(15.0)	6.9	(15.9)	
Urinary incontinence								
Ultrasound-guided Brachytherapy	127	2.2	(6.9)	7.1	(14.0)	4.9	(14.4)	0.11
Hospital 1	66	2.0	(6.4)	7.9	(15.8)	5.9	(16.0)	*0.41*
Hospital 2	61	2.5	(7.5)	6.2	(11.7)	3.8	(12.5)	
MRI-guided Brachytherapy	56	4.8	(11.1)	6.2	(11.0)	1.4	(10.3)	
All patients	183	3.0	(8.5)	6.8	(13.1)	3.8	(13.4)	
Bowel problems								
Ultrasound-guided Brachytherapy	140	3.6	(5.9)	7.5	(9.2)	3.9	(9.1)	0.79
Hospital 1	68	2.9	(4.0)	6.4	(7.4)	3.5	(7.4)	*0.61*
Hospital 2	72	4.2	(7.2)	8.5	(10.6)	4.3	(10.4)	
MRI-guided Brachytherapy	59	4.0	(5.4)	8.3	(11.8)	4.3	(11.9)	
All patients	199	3.7	(5.7)	7.7	(10.0)	4.0	(10.0)	
Sexual function								
Ultrasound-guided Brachytherapy	132	36.3	(38.3)	51.5	(37.1)	15.2	(32.2)	0.36
Hospital 1	69	43.6	(40.1)	56.4	(36.6)	12.7	(29.2)	*0.35*
Hospital 2	63	28.2	(34.9)	46.2	(37.2)	18.0	(35.3)	
MRI-guided Brachytherapy	56	24.1	(32.1)***	34.9	(35.5)	10.8	(24.8)	
All patients	188	32.7	(36.9)	46.6	(37.3)	13.9	(30.2)	

Table 4. Mean treatment-related function scores at baseline, at 24 months after treatment and changes from baseline to 24 months for patients who completed responses at baseline and at 24-month follow-up.

	Patients Responding	Baseline Score	Baseline (SD)	24 Months Score	24 Months (SD)	Baseline to 24 month change Score	Baseline to 24 month change (SD)	P-value
Urinary obstruction/irritation								
Ultrasound-guided Brachytherapy	110	17.2	(11.2)	24.7	(15.3)	7.5	(14.5)	0.0009
Hospital 1	60	16.3	(9.5)	23.4	(13.1)	7.1	(13.0)	*0.79*
Hospital 2	50	18.3	(12.9)	26.2	(17.5)	7.9	(16.3)	
MRI-guided Brachytherapy	45	22.7	(12.9)*	21.1	(10.6)	-.62	(10.6)	
All patients	155	18.8	(11.9)	23.9	(14.1)	5.1	(14.0)	
Urinary incontinence								
Ultrasound-guided Brachytherapy	111	2.6	(7.3)	8.2	(13.7)	5.6	(13.9)	0.04
Hospital 1	58	2.1	(6.4)	9.3	(13.4)	7.2	(12.3)	*0.19*
Hospital 2	53	3.2	(8.3)	7.0	(14.1)	3.8	(15.3)	
MRI-guided Brachytherapy	47	4.0	(11.2)	5.1	(11.8)	1.1	(8.7)	
All patients	158	3.0	(8.6)	7.3	(13.2)	4.2	(12.7)	
Bowel problems								
Ultrasound-guided Brachytherapy	129	3.6	(5.9)	6.4	(9.5)	2.8	(9.2)	0.70
Hospital 1	70	2.6	(3.7)	5.8	(8.6)	3.2	(8.1)	*0.59*
Hospital 2	59	4.8	(7.7)	7.1	(10.5)	2.3	(10.4)	
MRI-guided Brachytherapy	53	3.9	(5.7)	7.2	(8.0)	3.4	(8.8)	
All patients	182	3.7	(5.9)	6.7	(9.1)	3.0	(9.1)	
Sexual function								
Ultrasound-guided Brachytherapy	114	38.1	(38.2)	55.8	(35.3)	17.9	(32.7)	0.51
Hospital 1	65	42.3	(39.6)	57.5	(35.7)	15.2	(30.3)	*0.36*
Hospital 2	49	32.5	(36.0)	53.5	(34.9)	21.0	(35.7)	
MRI-guided Brachytherapy	48	23.9	(31.8)***	38.0	(35.4)***	14.1	(26.7)	
All patients	162	33.9	(37.0)	50.5	(36.3)	16.6	(31.0)	

Table 5. Mean treatment-related function scores at baseline, at 36 months after treatment and changes from baseline to 36 months for patients who completed responses at baseline and at 36-month follow-up.

	Patients Responding	Baseline		36 Months		Baseline to 36 month change		
		Score	(SD)	Score	(SD)	Score	(SD)	P-value
Urinary obstruction/irritation								
Ultrasound-guided Brachytherapy	103	17.3	(10.9	20.7	(11.6)	3.5	(12.9)	0.80
Hospital 1	58	16.7	(9.6)	20.2	(11.5)	3.5	(12.2)	*0.93*
Hospital 2	45	18.0	(12.5	21.4	(11.8)	3.3	(13.8)	
MRI-guided Brachytherapy	36	22.8	(11.9	25.6	(14.6)	2.8	(16.0)	
All patients	139	18.7	(11.4	22.0	(12.6)	3.3	(13.7)	
Urinary incontinence								
Ultrasound-guided Brachytherapy	95	2.3	(6.8)	9.9	(16.7)	7.6	(15.6)	0.44
Hospital 1	54	2.0	(6.6)	11.7	(18.2)	9.6	(17.3)	*0.14*
Hospital 2	41	2.7	(7.1)	7.5	(14.3)	4.9	(12.9)	
MRI-guided Brachytherapy	41	4.1	(11.6)	9.5	(17.2)	5.4	(14.2)	
All patients	136	2.9	(8.5)	9.8	(16.8)	6.9	(15.2)	
Bowel problems								
Ultrasound-guided Brachytherapy	109	3.4	(5.4)	5.8	(6.4)	2.4	(7.0)	0.20
Hospital 1	61	2.8	(3.5)	5.6	(5.5)	2.8	(5.9)	*0.51*
Hospital 2	48	4.2	(7.2)	6.1	(7.4)	1.9	(8.2)	
MRI-guided Brachytherapy	44	3.8	(5.4)	4.7	(5.4)	.85	(6.0)	
All patients	53	3.5	(5.4)	5.5	(6.1)	2.0	(6.7)	
Sexual function								
Ultrasound-guided Brachytherapy	103	37.9	(38.8)	58.9	(37.2)	21.0	(33.4)	0.13
Hospital 1	59	42.0	(39.9)	62.7	(37.7)	20.7	(35.3)	*0.93*
Hospital 2	44	32.4	(36.9)	53.8	(36.3)	21.3	(31.1)	
MRI-guided Brachytherapy	42	26.2	(33.2)	38.2	(34.8)	12.0	(27.3)	
All patients	145	34.5	(37.5)	52.9	(37.6	18.4	(31.9)	

Table 6. Mean treatment-related function scores at baseline, at 48 months after treatment and changes from baseline to 48 months for patients who completed responses at baseline and at 48-month follow-up.

		Baseline		48 Months		Baseline to 48 month change		
	Patients Responding	Score	(SD)	Score	(SD)	Score	(SD)	P-value
Urinary obstruction/irritation								
Ultrasound-guided Brachytherapy	71	16.0	(11.3)	18.1	(10.8)	2.0	(12.3)	0.99
Hospital 1	43	15.6	(9.6)	19.3	(10.7)	3.6	(10.5)	*0.18*
Hospital 2	28	16.7	(13.5)	16.3	(10.9)	-.40	(14.4)	
MRI-guided Brachytherapy	25	26.4	(14.1)	28.4	(17.3)***	2.0	(20.5)	
All patients	96	18.8	(12.8)	20.8	(13.5)	2.0	(14.7)	
Urinary incontinence								
Ultrasound-guided Brachytherapy	70	2.6	(7.6)	9.7	(16.9)	7.1	(16.0)	0.28
Hospital 1	40	2.3	(7.0)	11.3	(19.0)	9	(16.9)	*0.26*
Hospital 2	30	3	(8.4)	7.7	(13.8)	4.7	(14.6)	
MRI-guided Brachytherapy	28	5.4	(13.5)	8.9	(16.6)	3.6	(11.9)	
All patients	98	3.4	(9.6)	9.5	(16.8)	6.1	(15.0)	
Bowel problems								
Ultrasound-guided Brachytherapy	79	3.0	(5.1)	4.4	(5.5)	1.4	(6.5)	0.67
Hospital 1	48	2.3	(3.3)	3.5	(4.2)	1.1	(4.6)	*0.62*
Hospital 2	31	3.9	(7.0)	5.8	(6.8)	1.9	(8.7)	
MRI-guided Brachytherapy	29	5.3	(6.2)	7.5	(9.8)*	2.2	(10.8)	
All patients	108	3.6	(5.5)	5.2	(7.0)	1.6	(7.8)	
Sexual function								
Ultrasound-guided Brachytherapy	70	39.0	(40.4)	57.8	(37.4)	18.7	(31.0)	0.16
Hospital 1	43	42.8	(41.1)	59.7	(36.1)	16.9	(31.4)	*0.54*
Hospital 2	27	33.1	(39.2)	54.7	(39.8)	21.6	(30.5)	
MRI-guided Brachytherapy	21	32.8	(34.7)**	41.3	(35.2)	8.5	(22.3)	
All patients	91	37.6	(39.0)	54.0	(37.4)	16.4	(29.4)	

Table 7. Mean treatment-related function scores at baseline, at 60 months after treatment and changes from baseline to 60 months for patients who completed responses at baseline and at 60-month follow-up.

	Patients Responding	Baseline Score	Baseline (SD)	60 Months Score	60 Months (SD)	Baseline to 60 month change Score	Baseline to 60 month change (SD)	P-value
Urinary obstruction/irritation								
Ultrasound-guided Brachytherapy	46	17.5	(10.5)	19.3	(8.3)	1.8	(11.6)	0.58
Hospital 1	29	17.2	(9.4)	19.9	(8.1)	2.7	(11.1)	*0.51*
Hospital 2	17	18.0	(12.3)	18.3	(9.0)	.33	(12.6)	
MRI-guided Brachytherapy	10	26.7	(16.3)*	31.1	(20.1)**	4.4	(20.9)	
All patients	56	19.1	(12.1)	21.4	(12.0)	2.3	(13.5)	
Urinary incontinence								
Ultrasound-guided Brachytherapy	45	2.4	(7.1)	11.8	(17.1)	9.3	(16.2)	0.83
Hospital 1	28	2.1	(6.3)	11.4	(19.0)	9.3	(18.2)	*0.98*
Hospital 2	17	2.9	(8.5)	12.4	(13.9)	9.4	(12.5)	
MRI-guided Brachytherapy	11	4.5	(10.4)	12.7	(18.5)	8.2	(11.7)	
All patients	56	2.9	(7.8)	12.0	(17.2)	9.1	(15.3)	
Bowel problems								
Ultrasound-guided Brachytherapy	46	3.3	(3.9)	6.0	(7.5)	2.7	(7.5)	0.49
Hospital 1	28	3.3	(3.6)	5.1	(5.1)	1.8	(5.2)	*0.29*
Hospital 2	18	3.2	(4.4)	7.4	(10.3)	4.2	(10.0)	
MRI-guided Brachytherapy	12	6.3	(5.5)	7.3	(6.9)*	1.0	(7.4)	
All patients	58	3.9	(4.4)	6.3	(7.4)	2.4	(7.4)	
Sexual function								
Ultrasound-guided Brachytherapy	36	36.9	(37.3)	65.1	(34.3)	28.2	(37.3)	0.10
Hospital 1	22	43.7	(39.2)	72.7	(29.6)	29.0	(36.3)	*0.87*
Hospital 2	14	26.2	(32.6)	53.2	(38.7)	27.0	(40.1)	
MRI-guided Brachytherapy	12	35.2	(35.2)**	44.4	(37.5)	9.3	(20.6)	
All patients	48	36.5	(36.4)	60.0	(35.9)	23.5	(34.7)	